

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
26 April 2001 (26.04.2001)

PCT

(10) International Publication Number  
**WO 01/28557 A1**

(51) International Patent Classification<sup>7</sup>: **A61K 31/405**,  
31/4045, C07D 209/12

(21) International Application Number: PCT/US00/28832

(22) International Filing Date: 18 October 2000 (18.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/159,997 18 October 1999 (18.10.1999) US

(71) Applicant (for all designated States except US): **UNIVERSITY OF CONNECTICUT** [US/US]; 263 Farmington Avenue, Farmington, CT 06032 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MAKRIYANNIS, Alexandros** [US/US]; 348G Foster Drive, Willimantic, CT 06226 (US). **DENG, Hongfeng** [CN/US]; Apt. 64, 1 Northwood Road, Storrs, CT 06268 (US).

(74) Agents: **YALE, Guy, D. et al.**; Alix, Yale & Ristas, LLP, 750 Main Street, Hartford, CT 06103 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published:**

- With international search report.
- With amended claims.

**Date of publication of the amended claims:** 7 June 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **CANNABIMIMETIC INDOLE DERIVATIVES**

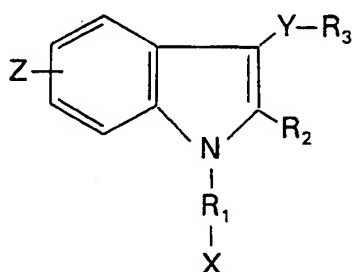
(57) Abstract: Novel cannabimimetic indole derivatives are presented which have preferentially high affinities for one of the cannabinoid CB1 or CB2 receptor sites. The improved receptor affinity makes these analogs therapeutically useful as medications in individuals and animals for treatment of pain, glaucoma, epilepsy, nausea associated with chemotherapy.

WO 01/28557 A1

## AMENDED CLAIMS

[received by the International Bureau on 6 April 2001 (06.04.01);  
original claims 1, 2 and 6 amended; new claim 15 added;  
remaining claims unchanged (3 pages)]

1. A compound of the formula:



and physiologically acceptable salts thereof wherein,

Z may be in the 4-, 5-, 6- or 7- position and is selected from the group consisting of nitroso, amino, alkylamino, dialkylamino, azido, cyano, and phenyl;

X is selected from the group consisting of halogen; hydrogen; hydroxy, low alkanoate, formyl, amino, cyano, isothiocyano and azido;

R<sub>1</sub> is selected from the group consisting of saturated or unsaturated straight carbon chains with a maximum length of seven carbon atoms, saturated or unsaturated branched carbon chains with a maximum length of seven carbon atoms, cyclic aliphatic rings interconnected to the indole-1 position with one or two carbon atoms, bicyclic aliphatic rings interconnected to the indole-1 position with one or two carbon atoms, and heterocyclic rings interconnected to the indole-1 position with one or two carbon atoms;

R<sub>2</sub> is selected from the group consisting of H and lower alkyl;

Y is selected from the group consisting of carbonyl and CH=CH (cis or trans); and

R<sub>3</sub> is selected from the group consisting of phenyl, naphthyl, 9-anthracenyl, phenyl with no more than two substituents selected from the group consisting of halogen, nitro, nitroso, amino, alkylamino, dialkylamino, hydroxy, methoxy, lower alkyl, azido, cyano and isothiocyano, naphthyl with no more than two substituents selected from the group consisting of halogen, nitro, nitroso, amino, alkylamino, dialkylamino, hydroxy, methoxy, lower alkyl, azido, cyano and isothiocyano and 9-anthracenyl with no more than two substituents selected from the group consisting of halogen, nitro, nitroso, amino, alkylamino,

dialkylamino, hydroxy, methoxy, lower alkyl, azido, cyano and isothiocyano.

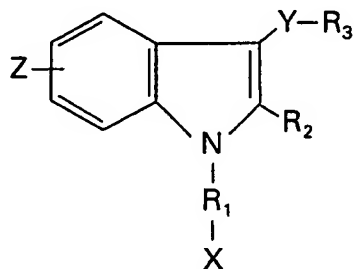
2. The compound of claim 1, wherein Z is in the indole-6 position and is selected from the group consisting of H, NO<sub>2</sub>, NH<sub>2</sub> and halogen.

3. The compound of claim 1, wherein Y is C≡O.

4. The compound of claim 1, wherein R<sub>1</sub> is an alkane with a maximum length of seven carbon atoms.

5. The compound of claim 1, wherein R<sub>2</sub> is selected from the group consisting of H and CH<sub>3</sub>.

6. A method of stimulating a cannabinoid receptor in an individual or animal comprising administering to the individual or animal a therapeutically effective amount of a compound having the formula:



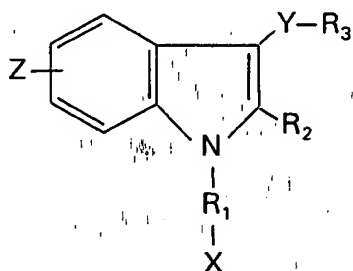
and physiologically acceptable salts thereof wherein,

Z may be in the 4-, 5-, 6- or 7- position and is selected from the group consisting of nitroso, amino, alkylamino, dialkylamino, azido, cyano, and phenyl;

X is selected from the group consisting of halogen, hydrogen, hydroxy, low alkanoate, formyl, amino, cyano, isothiocyano and azido;

R<sub>1</sub> is selected from the group consisting of saturated or unsaturated straight carbon chains with a maximum length of seven carbon atoms; saturated

15. A compound of the formula:



and physiologically acceptable salts thereof wherein,

Z may be in the 4-, 5- or 7- position and is selected from the group consisting of nitro, nitroso, amino, alkylamino, dialkylamino, azido, cyano, isothiocyano, and phenyl;

X is selected from the group consisting of halogen; hydrogen; hydroxy, low alkanoate, formyl, amino, cyano, isothiocyano and azido;

R<sub>1</sub> is selected from the group consisting of saturated or unsaturated straight carbon chains with a maximum length of seven carbon atoms, saturated or unsaturated branched carbon chains with a maximum length of seven carbon atoms, cyclic aliphatic rings interconnected to the indole-1 position with one or two carbon atoms, bicyclic aliphatic rings interconnected to the indole-1 position with one or two carbon atoms, and heterocyclic rings interconnected to the indole-1 position with one or two carbon atoms;

R<sub>2</sub> is selected from the group consisting of H and lower alkyl;

Y is selected from the group consisting of carbonyl and CH=CH (cis or trans); and

R<sub>3</sub> is selected from the group consisting of phenyl, naphthyl, 9-anthracenyl, phenyl with no more than two substituents selected from the group consisting of halogen, nitro, nitroso, amino, alkylamino, dialkylamino, hydroxy, methoxy, lower alkyl, azido, cyano and isothiocyano, naphthyl with no more than two substituents selected from the group consisting of halogen, nitro, nitroso, amino, alkylamino, dialkylamino, hydroxy, methoxy, lower alkyl, azido, cyano and isothiocyano and 9-anthracenyl with no more than two substituents selected from the group consisting of halogen, nitro, nitroso, amino, alkylamino, dialkylamino, hydroxy, methoxy, lower alkyl, azido, cyano and isothiocyano.

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
26 April 2001 (26.04.2001)

PCT

(10) International Publication Number  
**WO 01/28557 A1**

(51) International Patent Classification<sup>7</sup>: **A61K 31/405**,  
31/4045, C07D 209/12

(21) International Application Number: PCT/US00/28832

(22) International Filing Date: 18 October 2000 (18.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/159,997 18 October 1999 (18.10.1999) US

(71) Applicant (for all designated States except US): **UNIVERSITY OF CONNECTICUT** [US/US]; 263 Farmington Avenue, Farmington, CT 06032 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MAKRIYANNIS**, Alexandros [US/US]; 348G Foster Drive, Willimantic, CT 06226 (US). **DENG, Hongfeng** [CN/US]; Apt. 64, 1 Northwood Road, Storrs, CT 06268 (US).

(74) Agents: **YALE**, Guy, D. et al.; Alix, Yale & Ristas, LLP, 750 Main Street, Hartford, CT 06103 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG)!

**Published:**

- With international search report.
- With amended claims.

Date of publication of the amended claims: 7 June 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CANNABIMIMETIC INDOLE DERIVATIVES

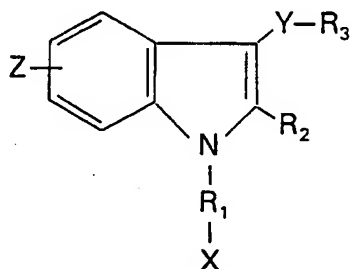
(57) Abstract: Novel cannabimimetic indole derivatives are presented which have preferentially high affinities for one of the cannabinoid CB1 or CB2 receptor sites. The improved receptor affinity makes these analogs therapeutically useful as medications in individuals and animals for treatment of pain, glaucoma, epilepsy, nausea associated with chemotherapy.

WO 01/28557 A1

## AMENDED CLAIMS

[received by the International Bureau on 6 April 2001 (06.04.01);  
original claims 1, 2 and 6 amended; new claim 15 added;  
remaining claims unchanged (3 pages)]

1. A compound of the formula:



and physiologically acceptable salts thereof wherein,

Z may be in the 4-, 5-, 6- or 7- position and is selected from the group consisting of nitroso, amino, alkylamino, dialkylamino, azido, cyano, and phenyl;

X is selected from the group consisting of halogen; hydrogen; hydroxy, low alkanoate, formyl, amino, cyano, isothiocyano and azido;

R<sub>1</sub> is selected from the group consisting of saturated or unsaturated straight carbon chains with a maximum length of seven carbon atoms, saturated or unsaturated branched carbon chains with a maximum length of seven carbon atoms, cyclic aliphatic rings interconnected to the indole-1 position with one or two carbon atoms, bicyclic aliphatic rings interconnected to the indole-1 position with one or two carbon atoms, and heterocyclic rings interconnected to the indole-1 position with one or two carbon atoms;

R<sub>2</sub> is selected from the group consisting of H and lower alkyl;

Y is selected from the group consisting of carbonyl and CH=CH (cis or trans); and

R<sub>3</sub> is selected from the group consisting of phenyl, naphthyl, 9-anthracenyl, phenyl with no more than two substituents selected from the group consisting of halogen, nitro, nitroso, amino, alkylamino, dialkylamino, hydroxy, methoxy, lower alkyl, azido, cyano and isothiocyano, naphthyl with no more than two substituents selected from the group consisting of halogen, nitro, nitroso, amino, alkylamino, dialkylamino, hydroxy, methoxy, lower alkyl, azido, cyano and isothiocyano and 9-anthracenyl with no more than two substituents selected from the group consisting of halogen, nitro, nitroso, amino, alkylamino,



dialkylamino, hydroxy, methoxy, lower alkyl, azido, cyano and isothiocyano.

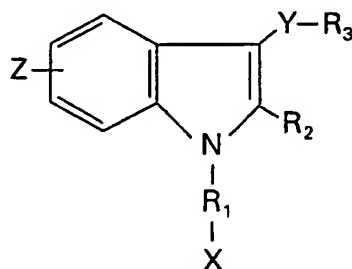
2. The compound of claim 1, wherein Z is in the indole-6 position and is selected from the group consisting of H, NO<sub>2</sub>, NH<sub>2</sub> and halogen.

3. The compound of claim 1, wherein Y is C=O.

4. The compound of claim 1, wherein R<sub>1</sub> is an alkane with a maximum length of seven carbon atoms.

5. The compound of claim 1, wherein R<sub>2</sub> is selected from the group consisting of H and CH<sub>3</sub>.

6. A method of stimulating a cannabinoid receptor in an individual or animal comprising administering to the individual or animal a therapeutically effective amount of a compound having the formula:



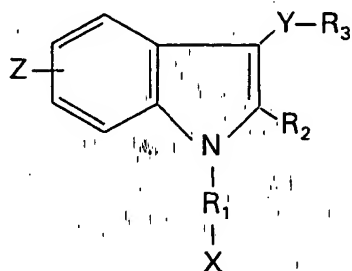
and physiologically acceptable salts thereof wherein,

Z may be in the 4-, 5-, 6- or 7- position and is selected from the group consisting of nitroso, amino, alkylamino, dialkylamino, azido, cyano, and phenyl;

X is selected from the group consisting of halogen, hydrogen, hydroxy, low alkanoate, formyl, amino, cyano, isothiocyano and azido;

R<sub>1</sub> is selected from the group consisting of saturated or unsaturated straight carbon chains with a maximum length of seven carbon atoms; saturated

15. A compound of the formula:



and physiologically acceptable salts thereof wherein,

Z may be in the 4-, 5- or 7- position and is selected from the group consisting of nitro, nitroso, amino, alkylamino, dialkylamino, azido, cyano, isothiocyano, and phenyl;

X is selected from the group consisting of halogen; hydrogen; hydroxy, low alkanoate, formyl, amino, cyano, isothiocyano and azido;

R<sub>1</sub> is selected from the group consisting of saturated or unsaturated straight carbon chains with a maximum length of seven carbon atoms, saturated or unsaturated branched carbon chains with a maximum length of seven carbon atoms, cyclic aliphatic rings interconnected to the indole-1 position with one or two carbon atoms, bicyclic aliphatic rings interconnected to the indole-1 position with one or two carbon atoms, and heterocyclic rings interconnected to the indole-1 position with one or two carbon atoms;

R<sub>2</sub> is selected from the group consisting of H and lower alkyl;

Y is selected from the group consisting of carbonyl and CH=CH (cis or trans); and

R<sub>3</sub> is selected from the group consisting of phenyl, naphthyl, 9-anthracenyl, phenyl with no more than two substituents selected from the group consisting of halogen, nitro, nitroso, amino, alkylamino, dialkylamino, hydroxy, methoxy, lower alkyl, azido, cyano and isothiocyano, naphthyl with no more than two substituents selected from the group consisting of halogen, nitro, nitroso, amino, alkylamino, dialkylamino, hydroxy, methoxy, lower alkyl, azido, cyano and isothiocyano and 9-anthracenyl with no more than two substituents selected from the group consisting of halogen, nitro, nitroso, amino, alkylamino, dialkylamino, hydroxy, methoxy, lower alkyl, azido, cyano and isothiocyano.